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TOWNSEND and TOWNSEND and CREW LLP

By: Dan Hall

PATENT
Attorney Docket No. 02307O-115611US
Client Ref. No. 2000-094-3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Deanna L. KROETZ et al.

Application No.: 10/694,641

Filed: October 27, 2003

For: INHIBITORS OF EPOXIDE HYDROLASES FOR THE TREATMENT OF HYPERTENSION

Confirmation No. 4011

Examiner: Brian Yong Kwon

Technology Center/Art Unit: 1614

REPLY BRIEF UNDER 37 CFR §41.41

Mail Stop Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Under the provisions of 37 C.F.R. § 41.41, this Reply Brief is being filed in Response to the Examiner's Answer mailed March 6, 2009. This Brief is timely filed on or before the two-month due date of May 6, 2009. A Request for Oral Hearing with required fee consistent with 37 C.F.R. § 41.47 is being filed in connection with this Brief.

2. RELATED APPEALS AND INTERFERENCES

The Examiner states that the Appeal Brief does not contain a statement identifying related appeal or interferences. Appellants respectfully direct the Examiner and the Honorable Board to Section 2 of the Appeal Brief where Appellants indicated that there are no related Appeals and interferences by the word "NONE".

Appellants affirm with this Reply Brief that there are no related Appeals and interferences.

3. STATUS OF CLAIMS

As correctly acknowledged by the Examiner, there are two (2) claims pending in the application, namely, claims 46 and 48.

4. STATUS OF AMENDMENTS

In the amendment submitted on November 26, 2008 in response to the Final Rejection mailed on September 17, 2008, Appellants requested cancellation of claims 47 and 49-53. This amendment was subsequently entered and only pending claims 46 and 48 are on appeal.

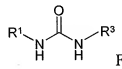
The Examiner's Answer states that Appellants' statement of the status of amendments after Final Rejection contained in the Appeal Brief is incorrect. The Answer further states that the amendment after Final Rejection filed on November 26, 2008 was acknowledged and entered in the Advisory Action mailed on December 12, 2008.

Appellants note that the Appeal Brief was submitted on December 9, 2008, prior to the issuance of the Advisory Action on December 12, 2008 advising that the Amendment was entered. Accordingly, in the absence of certainty that the Amendment would be entered, the Appeal Brief referred to all claims then pending. The Examiner's Answer mailed on March 6, 2009 correctly states that the Final Rejection filed on November 26, 2008 was acknowledged and entered in the Advisory Action mailed on December 12, 2008.

5. SUMMARY OF CLAIMED SUBJECT MATTER

A. CLAIM 46 – INDEPENDENT

The subject matter of claim 46 is directed to a method of reducing blood pressure in a patient by administering to the patient a therapeutically effective amount of an inhibitor of soluble epoxide hydrolase (sEH). In the claimed method, the inhibitor is a compound having the structure of Formula I or a pharmaceutically acceptable salt thereof:



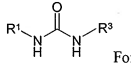
Formula I

wherein R^1 and R^3 are each independently selected from the group consisting of C_1-C_{20} and are substituted or unsubstituted alkyl, cycloalkyl, aryl, acyl, and heterocyclic.

Appellants' invention is based in part, on the discovery that inhibiting the enzymatic activity of sEH results in decreased blood pressure. The specification teaches, and the data in the application demonstrate that *in vivo* inhibition of sEH enzyme activity reduces blood pressure. Expressly recited and required elements of the claimed method are administration of (i) a functionally described inhibitor of sEH (ii) in a therapeutically effective amount (iii) wherein the inhibitor of sEH is further structurally characterized by Formula I, depicted above, and wherein both of the R substituents are independently C_1-C_{20} and substituted or unsubstituted alkyl, cycloalkyl, aryl, acyl, and heterocyclic.

B. CLAIM 48 – INDEPENDENT

The subject matter of claim 48 is directed to a method of reducing hypertension in a patient. The method comprises administering to the patient a therapeutically effective amount of an inhibitor of soluble epoxide hydrolase. In the claimed method, the inhibitor is a compound having the structure of Formula I or a pharmaceutically acceptable salt thereof:



Formula I

wherein R^1 and R^3 are each independently selected from the group consisting of C_1-C_{20} and are substituted or unsubstituted alkyl, cycloalkyl, aryl, acyl, and heterocyclic.

Again, the Appellants have discovered that inhibiting the enzymatic activity of sEH results in decreased hypertension. The specification teaches, and the data in the application demonstrate that *in vivo* inhibition of sEH enzyme activity reduces hypertension. Expressly recited and required elements of the claimed method are administration of (i) a functionally described inhibitor of sEH (ii) in a therapeutically effective amount (iii) wherein the inhibitor of sEH is further structurally characterized by Formula I, depicted above, and wherein both of the R substituents are independently C_1-C_{20} and substituted or unsubstituted alkyl, cycloalkyl, aryl, acyl, and heterocyclic.

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

As acknowledged by the Examiner's Answer, the sole issue to be resolved on appeal is the rejection of claims 46 and 48 under 35 U.S.C. § 102(e) as being allegedly anticipated by U.S. Patent No. 5,962,455 (hereinafter "Blum").

7. ARGUMENT

The claimed invention is based in part on Appellants' discovery that inhibiting the enzymatic activity of sEH results in reduced hypertension and/or reduced blood pressure. As stated above, the required and expressly recited elements of the claimed methods are administration of (1) a functionally described inhibitor of sEH (2) in a therapeutically effective amount (3) wherein the sEH inhibitor is further characterized by Formula I. At least the first two elements, namely administration of (1) a functionally described inhibitor of sEH (2) in a therapeutically effective amount, are not disclosed either explicitly or inherently by Blum.

Appellants respectfully maintain that the Examiner is improperly ignoring the functional language in the claims. Instead, the Examiner appears to be focusing solely on the structural limitations of the claims. In the Answer mailed on March 6, 2009, the Examiner reiterates his position that the R^1 and R^3 groups in the claims should be interpreted so that the phrase "C_1-C_{20} substituted or unsubstituted" does not limit the terms "cycloalkyl," "aryl," "acyl," and "heterocyclic." *See*, the Examiner's Answer at page 5 bridging to page 6. Based on this interpretation, the Examiner states that compounds in Blum read on the structural formula of the instant claims and alleges that Blum anticipates the instant claims because Blum teaches use of substituted benzylamine derivative compounds to treat cardiovascular diseases such as hypertension or essential hypertension as well as congestive heart failure. *See*, the Examiner's Answer at page 4 bridging to page 5.

This rejection is based on an assertion of inherency. The appealed claims require that the compounds of structural Formula I (1) have the function of being sEH inhibitors and (2) inhibit sEH when administered in a therapeutically effective amount. Blum does not expressly discuss sEH inhibition for its disclosed compounds. Therefore, this rejection logically can only be applied to the extent that Blum's compounds ***necessarily*** act as sEH inhibitors when administered in the amounts disclosed by Blum (*e.g.*, the doses disclosed in Blum at column 10, lines 47-55). The interpretation of the R^1 and R^3 groups in the present claims is not germane to this appeal as it is not relied upon by Appellants in their Appeal Brief or in this Reply Brief.

Accordingly, Appellants' Reply Brief will focus on the first two required and expressly recited elements of claims 46 and 48 and whether these elements are inherently met by Blum.

A. Legal Standard For Establishing an Anticipation Rejection under 35 U.S.C. § 102

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros., Inc. v. Union Oil Co.*, 814 F.2d 628, 631 (Fed. Cir. 1987).

"In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic ***necessarily*** flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (BPAI 1990) (emphasis in original). "The mere fact that a certain thing ***may*** result from a given set of circumstances is not sufficient [to establish inherency]." *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (emphasis and alteration in original) (citing *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981)). *See also*, M.P.E.P. § 2112 (IV); *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (stating that "[t]o establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is ***necessarily present*** in the thing described in the reference, ***and that it would be so recognized by persons of ordinary skill***. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient" (emphasis added)).

This standard applies to functional limitations as well. "The examiner must provide some evidence or scientific reasoning to establish the reasonableness of the examiner's belief that ***the functional limitation*** is an inherent characteristic of the prior art" before the burden is shifted to the applicant to disprove the inherency. *Ex parte Skinner*, 2 USPQ2d 1788, 1789 (BPAI 1986) (emphasis added). This long standing legal standard was reaffirmed by the Honorable Board recently in *Ex parte Whalen II*, 89 USPQ2d 1078 (BPAI 2008) (precedential) (Grimes, APJ) (copy attached). In *Whalen II*, the examiner raised a rejection under 35 U.S.C. § 102(b) alleging "that the compositions taught by [prior art] 'inherently possess the same

viscosity' as the claimed composition because they 'comprise similar components[s] used in overlapping ranges of concentrations as those claimed.' " *Whalen II*, 89 USPQ2d at 1082. The Examiner in *Whalen II* admitted that the cited prior art did not recite the claimed viscosity. *Id.* An expanded panel of the Board, including Chief Administrative Patent Judge Fleming, reversed the Examiner's finding of inherent anticipation, stating that, "[t]he Examiner has not provided evidence or scientific reasoning to show that any specific composition disclosed by [the cited prior art] is within the scope of the instant claims, and therefore has not made out a case of inherent anticipation by [the prior art]." *Ex parte Whalen II*, 89 USPQ2d at 1083. In doing so, the panel reiterated the requirement that the burden is on the Examiner to prove the inherent anticipation of each and every element recited in the claim, ***including functional elements***:

> Inherency ... may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981). See also *Ex parte Skinner*, 2 USPQ2d 1788, 1789 (BPAI 1986) ("[T]he examiner must provide some evidence or scientific reasoning to establish the reasonableness of the examiner's belief that ***the functional limitation*** is an inherent characteristic of the prior art" before the burden is shifted to the applicant to disprove the inherency.). (emphasis added)

Id.

B. The Examiner Has Not Met His Burden in Establishing an Anticipation Rejection under 35 U.S.C. § 102

a) Element 1 — Administration of an Inhibitor of sEH

The claimed invention expressly recites and requires reducing blood pressure or reducing hypertension in a patient by administering to the patient an inhibitor of soluble epoxide hydrolase (sEH). Administration of an inhibitor of sEH is a functional limitation required by the instant claims. To support the present anticipation rejection, the Examiner must prove that it is explicitly or inherently described in the cited Blum reference.

Similar to the facts in *Whalen II*, the present Examiner concedes that Blum is silent about the functional ability of Blum's substituted benzylamine derivative compounds to

inhibit sEH, but alleges that such property or characteristic is inherent in the compounds of Blum because they are allegedly encompassed by the claimed structural Formula I:

> Blum teaches use of compounds represented by the instant formula (e.g., RN 202472-67-1, RN 202472-68-2, RN 202472-69-3, RN 202472-70-6, etc...) or their salt for the treatment of cardiovascular disease including hypertension or essential hypertension as well as congestive heart failure, wherein said compound is administered in dosage amounts of from about 0.1 mg to about 140 mg per kilograms [sic] of body weight per day and in various dosage forms including oral dosage form (abstract; column 8, line 52 thru column 10, line 62).
>
> Although Blum is silent about the functional characteristic of said compounds in inhibiting soluble epoxide hydrolase, such property or characteristic deems [sic] to be inherent to the compounds disclosed by Blum which read on the claimed structure compounds. Thus, Blum anticipates the claimed invention.

Page 10 of the Office Action mailed on December 29, 2005. *See also, e.g.*, page 11 of the Office Action mailed on August 23, 2006.

Such a rejection is simply a conclusory allegation and is totally absent of any evidence or scientific reasoning to support the premise of the rejection that any compound that reads on Formula I is ***necessarily*** a sEH inhibitor. Without the required supporting evidence or scientific reasoning, the Examiner cannot meet his burden for alleging inherent anticipation of the claimed methods based on the disclosure of Blum.

In fact, the evidence of record in this case shows that the compounds of Blum do not inhibit sEH. As discussed in the Appeal Brief and in the response submitted on June 2, 2008, Blum discloses substituted benzylamine derivative compounds that ***selectively bind*** to mammalian Neuropeptide Y1 receptors (NPY1R) and inhibit the activity of Neuropeptide Y. Blum at column 1, lines 10-13 (emphasis added). The Examiner has provided no evidence that the NPY1R (which is a receptor involved in vasoconstriction, *see* Blum, column 1, lines 23-25) and the sEH enzyme (which catalyzes the hydrolysis of epoxyeicosatrienoic acids (EETs) to the corresponding dihydroxyeicosatrienoic acids (DHETs), *see*, Appellants' Appeal Brief at pages 12-13) are in any way functionally related. Moreover, Appellants have already provided evidence that the two proteins are structurally completely unrelated *See, e.g.*, BLAST

alignments submitted as Exhibits IIC-E with the Appeal Brief. Therefore, there is no evidence of record in this case that compounds that are selected to bind to NPY1R will bind to sEH at all. In order for the substituted benzylamine derivative compounds of Blum to operate as inhibitors of sEH, as proposed by the Examiner, they would not only need to bind to sEH, which is structurally unrelated to NPY1R, but also interfere with the active site within sEH responsible for epoxide hydrolase activity. Thus, in view of the uncontested evidence that NPY1R and sEH are functionally and structurally completely unrelated, a rejection based on the assertion that an inhibitor of NPY1R ***necessarily*** inhibits sEH cannot be maintained.

b) Element 2 — Inhibition of sEH When Administered in a Therapeutically Effective Amount

The claimed methods also require that a therapeutically effective amount of a sEH inhibitor be administered. The Examiner has also failed to provide evidence or reasoning to show that this element is disclosed in Blum.

The Examiner attempts to use Dr. Hammock's Declaration to prove that the Blum compounds provided therapeutic benefit as required by the pending claims:

> Dr. Hammock stated that the referenced compounds (e.g., compound RN 202472-69-3 and RN 202472-70-6) could be "mediocre activity" (see page 7 of Declaration filed 06/13/06). In other words, it is clear from Dr. Hammock's statement that the compounds of Blum possess some degree (little to moderate) of sEH inhibitor activity. Since the instant claims 46 and 48 do not specifically recite how much of sEH enzymatic activity is required to practice the claimed invention, the prior art directing the administration of the same compound in overlapping dosage amounts (see "0.001 μM/kg to about 100 mg/kg body weight" in para. [0060] of the instant specification) inherently possessing therapeutic effects for the same ultimate purpose (e.g., the treatment of hypertension) as disclosed by the applicant clearly anticipates the claimed invention even absent explicit recitation of underlying mechanism.
>
> Page 6 of Examiner's Answer (emphasis in original).

The Examiner does not consider the fact that the claims require the administration of ***a therapeutically effective amount*** of an inhibitor of sEH. The dosage levels for the

substituted benzylamine derivative compounds disclosed by Blum, *e.g.*, at column 10, lines 47-55, are relevant to the selected-for function of the compounds to bind to NPY1R and inhibit the activity of Neuropeptide Y. There is no evidence of record to suggest that the doses of the substituted benzylamine derivative compounds disclosed in Blum could inhibit she to any extent. To the extent that Blum's substituted benzylamine derivative compounds bind to or inhibit sEH at all, there is no evidence of record to suggest that they do so in physiologically relevant amounts. That is, administration of physiologically acceptable or therapeutically effective amounts of Blum's substituted benzylamine derivative compounds should bind to NPY1R and inhibit the activity of Neuropeptide Y, but there is no evidence to suggest that they will ***necessarily*** bind to or inhibit sEH at these levels.

Moreover, the Examiner has taken Dr. Hammock's statements out of context. In fact, as explained below, Dr. Hammock clearly shows that Blum's compounds, when administered at physiologically relevant amounts as taught by Blum almost certainly ***do not*** inhibit sEH.

In his Declaration dated May 30, 2006, Dr. Hammock made the following predictions based on his extensive experience in the area of sEH inhibition:

- with regard to RN 202472-67-1, Dr. Hammock states that "[t]here is a ***slight chance*** the group on the left of the urea would yield activity ***with the correct substituents on the other side***. However, the activity should be mediocre to poor." (emphasis added)
- with regard to RN 202472-68-2, Dr. Hammock states that "This compound is similar to [RN202472-67-1] except that the sides are reversed. ***For the same reasons as set forth with the respect to the preceding compound***, I predict that this compound would have ***poor to no activity*** as an inhibitor of sEH." (emphasis added).
- with regard to RN 202472-69-3, Hammock states that "[t]here is a ***chance*** that this compound could be of mediocre activity" (emphasis added).

See, Dr. Hammock's Declaration at pages 6-7.

In particular, Dr. Hammock explained in his Declaration that "many otherwise inactive compounds are capable of inhibiting an enzyme's activity if present at concentrations beyond those that can be achieved *in vivo*," *i.e.*, amounts that are not physiologically acceptable or therapeutically effective. *See*, Dr. Hammock's Declaration at page 2. Indeed, Dr. Hammock affirmatively states that none of the compounds of Blum would be expected to inhibit sEH at physiologically relevant concentrations as they were designed to bind to the Neuropeptide Y1 receptor. *See*, Dr. Hammock's Declaration at pages 8-9.

However, inherency requires a showing that the compounds ***necessarily*** possess the sEH inhibitory activity at therapeutically effective amounts, not that they ***may*** or have a chance to inhibit sEH when administered at or above therapeutically effective amounts. Therefore, Dr. Hammock's statements not only fail to support the Examiner's position but provide powerful evidence against a finding of inherency as alleged by the Examiner.

c) The Examiner Has Not Met the Burden to Show that Blum Inherently Discloses Compounds that Inhibit sEH in Therapeutically Effective Amounts

The examiner must provide some evidence or scientific reasoning to establish the reasonableness of the examiner's belief that the functional limitation is an inherent characteristic of the prior art before the burden is shifted to the applicant to disprove a *prima facie* showing of inherency. *Ex parte Skinner*, 2 USPQ2d at1789. For the reasons discussed above and in Appellants' Appeal Brief, the Examiner has not met this burden.

Regardless, without conceding that the Examiner has properly set forth a *prima facie* case of inherency, Appellants have effectively rebutted the Examiner's allegations with evidence showing that the substituted benzylamine derivative compounds of Blum do not ***necessarily*** inhibit sEH in therapeutically effective amounts, to the extent that they inhibit sEH at all. Appellants have shown that the Neuropeptide Y1 receptor (NPY1R) and sEH enzyme both are structurally and functionally unrelated. Therefore, compounds that are selected to bind to NPY1R in therapeutically effective amounts will not ***necessarily*** bind to sEH and almost certainly do not inhibit sEH in therapeutically effective amounts. Dr. Hammock's expert Declaration affirmatively confirms that ***none*** of the compounds of Blum would be expected to

inhibit sEH at physiologically relevant concentrations as they were designed to bind to the Neuropeptide Y1 receptor. *See, e.g.*, Dr. Hammock's Declaration at pages 8-9.

The Examiner cannot ignore the functional limitation that the compound(s) administered in the present methods must have sEH inhibitory activity in a therapeutically effective amount, which, as required by *Ex parte Skinner* and *Ex parte Whalen II, supra*, must be met by the prior art explicitly or inherently before anticipation can be found.

In summary, Appellants submit that the Examiner has not met his burden of establishing an anticipation rejection under 35 U.S.C. § 102(e) based on an inherency theory.

8. CONCLUSION

For the foregoing reasons as well as reasons set forth in Appellants' Appeal Brief, Appellants respectfully submit that the rejection under 35 U.S.C. § 102(e) based on Blum is in error. It is respectfully requested that the Honorable Board reverse the Examiner's final rejection of claims 46 and 48.

Respectfully submitted,

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